REMARKS

Reconsideration is requested.

The specification has been revised to include definitions of saccharides described in WO02/39979, as translated in US 2004/0028635 (of record) in ¶[0023]-[0029], [0031]-[0034] and [0036], which describe oligosaccharides and polysaccharides and which are referred to in the paragraph spanning lines 5-10 of the originally-filed specification. Specifically, the originally-filed specification describes saccharides of the present invention as follows:

> "The hydrophilic segment that is saccharide in nature is a natural or synthetic oligosaccharide or polysaccharide, that may or may not be modified, as defined in application WO 02/39979. It is advantageously dextran, where appropriate sulfated, or heparin."

The saccharides of application WO 02/39979 which are believed to be incorporated-by-reference in the originally-filed application by way of the above-quoted paragraph have been included in the specification by the above amendments.

The effective date of Rule 57 is October 21, 2004 (see 69 FR 56481 dated September 21, 2004). As the present application is a U.S. national phase of a PCT application filed June 10, 2003, the following description of incorporation-by-reference, as found in MPEP § 608.01(p) (Rev. 2, May 2004) (see www.uspto.gov) applies to the present application:

> I. INCORPORATION BY REFERENCE
> The *>Director< has considerable discretion in determining what may or may not be incorporated by reference in a patent application. General Electric Co. v. Brenner, 407 F.2d 1258, 159 USPQ 335 (D.C. Cir. 1968). The incorporation by reference practice with respect to applications which issue

as U.S. patents provides the public with a patent disclosure which minimizes the public's burden to search for and obtain copies of documents incorporated by reference which may not be readily available. Through the Office's incorporation by reference policy, the Office ensures that reasonably complete disclosures are published as U.S. patents. The following is the manner in which the *>Director< has elected to exercise that discretion. Section A provides the guidance for incorporation by reference in applications which are to issue as U.S. patents. Section B provides guidance for incorporation by reference in benefit applications; i.e., those domestic (35 U.S.C. 120) or foreign (35 U.S.C. 119(a)) applications relied on to establish an earlier effective filing date. >See MPEP § 2181 for the impact of incorporation by reference on the determination of whether applicant has complied with the requirements of 35 U.S.C. 112, second paragraph when 35 U.S.C. 112, sixth paragraph is invoked.<

A. Review of Applications Which Are To Issue as Patents.
An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, Ex parte *>Schwarze<, 151 USPQ 426 (Bd. Ape. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below.

"Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application.

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2. Improper Incorporation
The filing date of any application wherein essential material is improperly incorporated by reference to a foreign

> application or patent or to a publication will not be affected because of the reference. In such a case, the applicant will be required to amend the spec-ification to include the material incorporated by reference.
> ...
>
> The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The concurrently-filed Declaration is submitted in accordance with the above-quoted requirements of MPEP § 608.01(p) (May 2004). The above amendments to the specification consists of the same material incorporated by reference in the referencing application.

Claims 1, 2 and 5-23 are pending. Claims 7, 11-14, 17 and 18 have been withdrawn from consideration. Claim 1 has been revised to define the compound components of the elected species, to advance prosecution. Claim 1 further includes saline (an aqueous medium), as disclosed, for example, on page 6, lines 24-27 of the specification. No new matter has been added.

New claim 20 finds support in claim 1. Claims 20-23 have been added to define further patentable aspects of the disclosed invention. Claims 21-23 are based on the amended passages of the specification. Support for the claims is believed to be found

in the originally-filed specification, as noted for example in the concurrently filed DECLARATION PURSUANT TO MPEP §608.01(p)I.A.2.[1]

Claim 4 has been canceled, without prejudice.

Claim 3 has been canceled, without prejudice, to advance prosecution by making moot the Section 112, second paragraph, and Section 103 rejections of claim 3. Withdrawal of the Section 112, second paragraph, of claim 3 and the Section 103 rejection of claim 3 over Chauvierre (WO 02/39979), Desai (U.S. Patent No. 6,096,331), Yen (U.S. Patent No. 5,616,311) and Bonsen (U.S. Patent No. 4,001,401) is requested.

The Section 103 rejection of claims 1-6, 8-10, 15-16 and 19 over Chauvierre (WO 02/39979 - equivalent to U.S. Patent Application Publication No. 2004/0028635) and Desai (U.S. Patent No. 6,096,331) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing comments, as well as the remarks of record.

The Examiner's consideration of U.S. Patent Application Publication No. 2004/0028635, and reference to the same in the Office Action of June 23, 2008, are acknowledged with appreciation. The Examiner's consideration of the applicants previously submitted Remarks and the Examiner's comments on pages 8-12 of the Office Action dated June 23, 2008 are similarly appreciated. The Examiner's

[1] Rev. 2, May 2004.

confirmation that Desai et al do not disclose that hemoglobin may be present in the polymeric shell of a heparin-coated particle, thereby providing a blood substitute[2].

The Examiner's comment that "the features upon which Applicant relies (i.e., the means by which hemoglobin is associated with the heparin polysaccharide) is not recited in the rejected claim(s)"[3] is not understood. Clarification is requested as claim 1 requires "said hemoprotein being non-covalently associated with said surface portion" and the "surface portion" is defined in claim 1 as "comprising an oligosaccharide or polysaccharide hydrophilic segment covalently linked via one of its ends to a single hydrophobic segment of formula (I), or via each of its two ends to a hydrophobic segment of formula (I), the two hydrophobic segments being the same or different, said core portion and said surface portion forming a sequenced block copolymer". Claim 1 therefore defines the non-covalent association of the hemoprotein, such as hemoglobin, with the saccharide, such as heparin.

One of ordinary skill in the art will understand that compounds may associate non-covalently, as opposed to, for example, covalent attachments or associations. The distinction is important and significant in view of the art relied upon by the Examiner. Specifically, the cited Desai patent fails to describe "the ultrasonic irradiation process

[2] See Advisory Action dated November 23, 2007 and page 10 of the Office Action dated June 23, 2008 ("Desai et al taught the synthesis of nanoparticles comprising synthetic block copolymers (column 10, lines 3-22), attached to biocompatible materials, i.e. polysaccharides (column 9, lines 42-49). Desai et al do not explicitly disclose heparin as a contemplated polysaccharide; however, absent evidence to the contrary, the art recognizes that heparin is a polysaccharide. Desai et al also contemplate that hemoglobin would be present in the polymeric shell (column 9, line 54; column 11, line 63), thereby providing a blood substitute.")

[3] See page 10 of the Office Action dated June 23, 2008.

described above" or further describe how hemoglobin is to "participate in the delivery of a biologic".

The cited Desai patent however is a continuation-in-part of U.S. Patent No. 5,916,596, which is a continuation-in-part of U.S. Patent No. 5,665,382. Each of the parent patents are incorporated-by-reference in the cited Desai patent.

U.S. Patent No. 5,665,382, (herein after Grinstaff) describes and claims methods of preparing pharmaceutically active agents for in vivo delivery. The claimed method of Grinstaff involves cross-linking disulfide bonds of a biocompatible material with high intensity ultrasound to form a polymeric shell of the crosslinked material which contains a pharmaceutically active agent **in** the polymeric shell. See claim 1 of Grinstaff for example.[4] The cross-linking reaction of Grinstaff, and by incorporation Desai, is a covalent attachment which is distinct from and would have made obvious the non-covalent association of the presently claimed invention.

Claim 4 of Grinstaff specifically includes hemoglobin as a protein biocompatible material containing cross-linkable disulfide bonds which may be used to form a polymeric shell of Grinstaff. Claim 3 of Grinstaff alternatively states that "polysaccharides containing sulfhydryl groups and/or disulfide groups" may be biocompatible materials which may be used to form a polymeric shell of Grinstaff.

The cited Desai patent therefore, in referring to hemoglobin in the passages of column 11 of the Desai patent reproduced in the applicants previous Remarks, will be

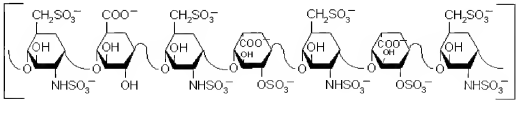
[4] The fact that the presently claimed invention allows for inclusion of active material in the recited particle does not suggest that it would have been obvious from the art to have associated a hemoprotein non-covalently with the surface portion of the particle as appears to be asserted by the Examiner. See pages 9 and 10, for example, of the Office Action dated June 23, 2008.

understood by one of ordinary skill in the art to be a reference to a polymeric shell formed of cross-linked hemoglobin. Alternatively, the cited Desai patent will be understood, from the whole of the patent and its incorporated-by-reference parent patent (i.e., Grinstaff), to relate to a polymeric shell formed of cross-linked polysaccharides containing disulfide or sulfhydryl groups.

Neither Desai nor Grinstaff teach or suggest a polymeric shell formed of cross-linked hemoglobin "coated with" (see Advisory Action dated November 23, 2007) or associated with heparin or any other saccharide or polysaccharide. Neither Desai nor Grinstaff teach or suggest a polymeric shell formed of cross-linked polysaccharides containing sulfhydryl groups associated with a protein, such as hemoglobin. The Examiner will appreciate that heparin is not a saccharide or polysaccharide containing sulfhydryl or disulfide groups[5], as would be required according to the teachings of Grinstaff and Desai to form a polymeric shell with high intensity ultrasound.

Moreover, Grinstaff further describes the aim and purpose of Desai's brief mention of hemoglobin polymeric shells in the following passage from column 19, line

[5] Heparin is a mucopolysaccharide with a molecular weight ranging from 6,000 to 40,000 Da. The average molecular of most commercial heparin preparations is in the range of 12,000 - 15,000. The polymeric chain is composed of repeating disaccharide unit of D-glucosamine and uronic acid linked by 1->4 interglycosidic bond. The uronic acid residue could be either D-glucuronic acid or L-iduronic acid. (Structure below) Few hydroxyl groups on each of these monosaccharide residues may be sulfated giving rise to a polymer with that is highly negatively charged. The average negative charge of individual saccharide residues is about 2.3.



22 through column 21, line 4 of Grinstaff reproduced in the Remarks of the applicants previous submission, which will be understood by one of ordinary skill in the art to clarify the vague reference in Desai to the use of hemoglobin polymeric shells as specific targeting or delivery agents. Specifically, Desai lists "physiologically active gasses", among the following broad genus of "biologic[s]" which may be delivered by the particles of polymeric shells (see column 9, lines 17-27 of Desai (as obtained from www.uspto.gov):

> As used herein, the term "biologic" refers to pharmaceutically active agents (such as analgesic agents, anesthetic agents, anti-asthamatic agents, antibiotics, anti-depressant agents, anti-diabetic agents, anti-fungal agents, anti-hypertensive agents, anti-inflammatory agents, anti-neoplastic agents, anxiolytic agents, enzymatically active agents, nucleic acid constructs, immunostimulating agents, immunosuppressive agents, physiologically active gases, vaccines, and the like), diagnostic agents (such as ultrasound contrast agents, radiocontrast agents, or magnetic contrast agents), agents of nutritional value, and the like.

The description in Grinstaff to the use of particles of hemoglobin crosslinked polymeric shells containing oxygen to deliver oxygen is consistent with, and further explains, the aim and intent and teaching of Desai in the only two instances where hemoglobin is mentioned as a crosslinkable material of the polymeric shell of Desai's particles.

The Examiner is again urged to appreciate that the presently claimed invention provides a product of nanoparticles which include a sequenced block polymer with a

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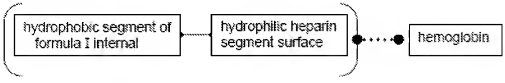
http://www.people.vcu.edu/~urdesai/hep.htm#Heparin%20-%20Structure

particle core comprising the hydrophobic segment of formula (I), and a heparin saccharide hydrophilic segment at the surface of the particle, which is in turn associated with hemoglobin at the surface of the particle. This structure may be simply illustrated, without limitations, as the following linear representation of a component of the claimed nanoparticles, wherein the structure in brackets forms the nanoparticles and the hemoglobin is associated with the surface which contains the hydrophilic heparin:



In contrast to the above non-limiting schematic of an embodiment of the presently claimed invention, Desai teaches a particle shell of preferably crosslinked albumin or other disulfide or sulfhydryl containing proteins, such as hemoglobin (as further elucidated by Grinstaff which is incorporated-by-reference in Desai), which may be used as a targeting agent for chemotherapeutic drugs or encapsulated oxygen (in the case of crosslinked hemoglobin polymeric shells). Neither Desai nor Grinstaff teach or suggest nanoparticles made of polymeric shells containing a combination of a sequenced block polymer of formula (I) of the present claims covalently linked to a saccharide, such as heparin, in a particle shell, which is non-covalently associated with a hemoprotein, such as hemoglobin.

The Examiner asserts that "Desai et al do not disclose whether the hemoglobin is covalently or non-covalently associated with the polysaccharide shell. Rather, covalent

bonding is optional (col. 11, lines 19-20)."[6] The applicants believe sufficient convincing remarks have been previously submitted to demonstrate that, in the case of hemoglobin, Desai describes cross-linked hemoglobin as a cross linked particle shell and that it would have been contrary to Desai to have non-covalently associated hemoglobin to a shell of a particle containing a saccharide hydrophilic segment.

The Examiner's reference to column 9, line 54 and column 11, line 63 of Desai for an alleged contemplation "that hemoglobin would be associated with the polymeric shell, ... thereby providing a blood substitute"[7] again refuses to view the whole of Desai, and the incorporated Gristaff patent.

Desai, at best, teaches the production of particles of crosslinked albumin, or other disulfide- or sulfhydryl-containing proteins (or disulfide- or sulfhydryl-containing saccharides such as hemoglobin) for delivery of encapsulated chemotherapeutics (or encapsulated oxygen in the case of the crosslinked "megameric" hemoglobin particles of Desai as elucidated by Grinstaff). Desai and Grinstaff teach that nanoparticles of Desai are, in one embodiment, crosslinked hemoglobin as hemoglobin contains cross-linkable sulfhydryl or disulfide groups and can be used not only to administer encapsulated oxygen but can also be used to transport oxygen in vivo as the ultrasonic crosslinking method of Desai/Grinstaff allegedly does not substantially diminish the native oxygen-exchange capacity of the hemoglobin. Desai therefore does not describe that "hemoglobin may be associated with the nanoparticle shell comprising a polysaccharide so as to be useful as a blood substitute" as previously stated by the

[6] See page 5 of the Office Action dated June 23, 2008.

Examiner or "polysaccharide-coated nanoparticles associated with hemoglobin" as stated by the Examiner in the Office Action of June 23, 2008. Heparin does not include disulfide or sulfhydryl groups and neither Desai nor Grinstaff describe heparin as a saccharide of their invention.

The Examiner has appreciated that nanoparticles of a sequenced block polymer of formula (I) of the present claims covalently linked to a saccharide were known in the art.[8] More specifically, the Examiner apprecaites that Chauvierre describes nanoparticles of the claims.[9] The present specification further refers to Chauvierre in describing the particles of the present claims.[10]

With respect to the structure of the nanoparticles of the present invention, which the Examiner understands to have been known in the art, Chauvierre teaches that (emphasis added): [11]

> [0039] In the specific case of particles and micelles, it is probable that the copolymer has a structure arranged as follows: the chains of the same nature, that is to say saccharide or hydrophobic chains, group together, either to form the core structure of the micelle or particle or the brush-like ring around this core structure. Their distribution between the core structure and the ring will, of course, depend on the nature, aqueous or organic, of the solvent in which the particles or micelles are dispersed. The term "brush-like ring" is intended to denote a structure in which

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[7] See page 5 and page 11 ("polysaccharide-coated nanoparticles associated with hemoglobin may be used as a blood substitute (e.g. Desai et al)") of the Office Action dated June 23, 2008.

[8] See page 10, ¶ ii) of the Office Action dated June 23, 2008.

[9] See page 5 of the Office Action dated June 23, 2008 ("Chauvierre et al teach the synthesis of nanoparticles of Inm to Imm [0045-46] comprising a core portion and a surface portion forming a sequenced block copolymer, said core portion comprising at least one hydrophobic segment having the formula as taught in Formula I, wherein "X" may be a "CN" moiety, wherein the hydrophobic segment may be a poly(alkylcyanoacrylate) [0010-0019], [0039] [0043-44] conjugated to a saccharide hydrophilic that may be heparin [0028].")

[10] See page 3, lines 20-29 of the present specificaiton.

[11] See reproduction of US 2004/0028635 available at www.uspto.gov.

> the segments constituting the ring are bonded via one of their ends to the segments constituting the core. Their free ends constitute the periphery of the ring. Thus, in aqueous medium, the hydrophobic segments are grouped together so as to form the core and the segments of saccharide nature are positioned in a brush-like ring all around this core. In a solvent or organic type, this arrangement between the two types of segment is reversed: the core is of hydrophilic nature and is thus formed of the segments of saccharide nature and the brush-like ring is of hydrophobic nature and is thus formed of the segments of general formula (I).

Moreover, Chauvierre teaches that the brush-like structure of the particles of the present claims are distingiished from, for example, nanoparticles based on amphiphilic block copolymers comprising dextran and poly(alkyl cyanoacrylate) segments derived from the anionic polymerization of cyanoacrylate monomers in the presence of dextran, which have grafted structures. Such grafted structures had been previously described by S. J. Douglas et al.; Journal of Controlled Release (1986), 15-23).[12]

The copolymers of the present invention are distinguished from grafted structure of the prior copolymers in that the grafted structures can not contain the brush-like ring structure in an aqueous medium as several hydrophobic segments are covalently bonded to a single chain of saccharide nature.[13] Chauvierre teaches that the block form of the copolymers distinguish the copolymers of the claims and provide the particles of the claims with their definative structure. More specifically, Chauvierre describes as how the block form of the claimed copolymer is inaccessible by the previously used anionic polymerization.[14] One of ordinary skill in the art will appreciate from, for example, Chauvierre that the block structure of the claimed particles do not include side

[12] See ¶[0005] of Chauvierre.
[13] See ¶[0040] of Chauvierre.

branches of saccharide nature on the hydrophobic segment or side branches of hydrophobic nature on the segment of saccharide nature, as would be found in a grafted structure.[15]

The claimed structure will be understood to inherently contain the "brush-like" structure, as described by Chauvierre.[16]

The non-covalent association of a hemoprotein with a surface portion of the particles of the invention, as claimed, would not have been obvious from the cited combination of art.

It is this "brush-like" structure inherent to the claimed structure that confers to the nanoparticles the long circulating life that is essential for their application as blood substitutes. There was no reasonable or predictable expectation of success from the cited references, or from the general knowledge in the art, that the surface properties of the nanoparticles, in particular their long- circulating life in blood, would not be negatively impacted if they were associated with hemoglobin.

The inventors demonstrated that the biding of haemoglobin to the heparin coated nanoparticles did not affect the spectral properties of the haemoprotein, since the main

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[14] See ¶[0006] - [0009] of Chauvierre.

[15] See ¶[0018] of Chauvierre. See also Bertholon et al. "Properties of Polysaccharides Grafted on Nanoparticles Investigated by EPR" Langmuir 2006, 22, 5485-5490; and Bertholon et al. "Characterization of Dextran - Poly(isobutylcyanoacrylate) Copolymers Obtained by Redox Radical and Anionic Emulsion Polymerization" Macromolecules 2006, 39, 3559-3567 (copies submitted herewith).

[16] The Examiner's repeated reference to In re Van Geuns, 26 USPQ2d 1057 (Fed. Cir. 1993) on pages 10 and 12 of the Office Action dated June 23, 2008 are noted. The appellant unsuccessfully argued in Van Geuns that a claim to a "magnet assembly" with a "uniform magnet field" was not limited to an NMR or MRI embodiments of the specification because limitations are not read into the claims from the specification. See 26 USPQ2d 1059. The facts of Van Geuns however are distinguished from the facts of the present applications in that the chemical components of the claimed invention necessarily form the structures described in Chauvierre whereas the "uniform magnet field" of Van Geuns could

characteristic peaks of haemoglobin CO were still present. These spectral characteristics together with the fact that the haemoglobin loaded heparin coated nanoparticles turned to the typical red color of haemoglobin after reduction with sodium dithionite and equilibration with CO were good indicators that haemoglobin maintained its capacity to exchange gas. Finally, results of zeta potential and of complement activation performed on the nanoparticles loaded with haemoglobin showed that the association of haemoglobin with the nanoparticle surface did not change the surface properties of the carrier, in terms of their zeta potential and of their complement activation properties, that are essential to define the fate of the nanoparticles m vivo after intravenous administration.[17]

These results are unexpected in view of, for example, the Desai patent, as elucidated by Grinstaff, which describes the unpredictability of hemoglobin-containing blood substitutes. Specifically, Grinstaff is believed to teach the importance of highly cross-linked hemoglobin polymer particles which is not required by and would be contrary to the presently claimed invention.

Similarly, there was no reasonable or predictable expectation of success that the hydrodynamic radius of these nanoparticles would not be negatively affected by association of hemoglobin at their surface. The inventors demonstrated that the size of nanoparticles containing heparin was not significantly affected by the association of

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apparently have been a "level of magnetic field uniformity" which would not have been required for NMR imaging and would have thus read on the art cited in Van Geuns.

[17] See Chauvierre et al. Cell. Molec. Biol., 2004, 50(3), 233-239 "A New Generation of Polymer Nanoparticles For Drug Delivery" (of record).

hemoglobin.[18] Moreover, there was no reasonable or predictable expectation of success that the associated hemoglobin would retain its capacity of transporting gases such as oxygen or carbon monoxide. The inventors have demonstrated that hemoglobin associated with the particles, as claimed, is functional.[19]

Finally, there was no reasonable or predictable expectation of success that the particles of the invention non-covalently associated with a hemoprotein would not activate complement. In fact, the applicants believe it would have been reasonable to expect that a hemoprotein associated with a surface saccharide of a particle would activate complement. The applicants believe the attached Andersson et al[20] demonstrates an expectation that the nascent C3b molecule of the complement pathway is able to bind specifically to proteins and carbohydrates via free hydroxyl or amino groups, forming covalent ester or amide bonds, respectively. The applicants believe that one of ordinary skill in the art would have expected that the either or both of the carbohydrates, such as dextran, or hemoproteins of the surface of the particles of the claims would activate complement. The applicants have demonstrated however that particles of the claims do not activate complement.[21]

The claimed invention provides unexpected and surprising advantages which are persuasive evidence that the claimed products would not have been obvious in view of the cited combination of art.

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[18] See Chauvierre et al, Biomaterials, 2004, 25, 3081-3086 "Heparin coated poly(alkylcyanoacrylate) nanoparticles coupled to hemoglobin: a new oxygen carrier" (of record).

[19] See fn 15 and 16.

[20] Andersson et al "Binding of C3 fragments on top of adsorbed plasma proteins during complement activation on a model biomaterial surface" Biomaterials 26 (2005) 1477-1485.

[21] See fn 15 and 16.

The claims are submitted to be patentable over the cited combination of art. Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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